

Patient-Reported Outcomes in Left Ventricular Assist Device Therapy

A Systematic Review and Recommendations for Clinical Research and Practice

Corline Brouwers, MSc; Johan Denollet, PhD; Nicolaas de Jonge, MD, PhD; Kadir Caliskan, MD; Jennifer Kealy; Susanne S. Pedersen, PhD

Background—Technological advancements of left ventricular assist devices (LVAD) have created today's potential for extending the lives of patients with end-stage heart failure. Few studies have examined the effect of LVAD therapy on patient-reported outcomes (PROs), such as health status, quality of life, and anxiety/depression, despite poor PROs predicting mortality and rehospitalization in patients with heart failure. In this systematic review, we provide an overview of available evidence on the impact of LVAD therapy on PROs and discuss recommendations for clinical research and practice.

Methods and Results—A systematic literature search identified 16 quantitative studies with a sample size ≥ 10 (mean \pm SD age = 50.1 ± 12.6 years) that examined the impact of LVAD therapy on PROs using a quantitative approach. Initial evidence suggests an improvement in health status, anxiety, and depression in the first few months after LVAD implantation. However, PRO scores of patients receiving LVAD therapy are still lower for physical, social, and emotional functioning compared with transplant recipients. These studies had several methodological shortcomings, including the use of relatively small sample sizes, and only a paucity of studies focused on anxiety and depression.

Conclusions—There is a paucity of studies on the patient perspective of LVAD therapy. To advance the field of LVAD research and to optimize the care of an increasingly growing population of patients receiving LVAD therapy, more well-designed large-scale studies are needed to further elucidate the impact of LVAD therapy on PROs. (*Circ Heart Fail.* 2011;4:714-723.)

Key Words: left ventricular assist device ■ patient-reported outcomes ■ quality of life ■ review

Worldwide heart transplantation offers hope to ≈ 3500 patients with advanced heart failure each year, but there are still $>15\,000$ patients on transplant waiting lists in urgent need of a donor heart.¹ Driven by this significant shortage of donor hearts and a simultaneous increase in the incidence of heart failure, the first concepts of mechanical circulatory support from the early 1970s have been transformed into highly advanced devices capable of long-term support for patients with end-stage heart failure. The most commonly used long-term devices are left ventricular assist devices (LVADs).^{2,3} Left ventricular assist devices can be divided into 2 main types: (1) the pulsatile pumps that mimic the natural pulsing action of the heart and (2) the continuous flow pumps that can be subdivided into either centrifugal or axial flow pumps.⁴

Editorial see p 680 Clinical Perspective on p 723

The primary focus of most LVAD studies has been on the clinical aspects of this therapy, including the efficacy of

different device types, device settings, and alternative therapies (eg, optimal medical treatment and heart transplantation) in enhancing survival and reducing complications. Only a subset of LVAD studies have examined the impact of LVAD therapy on patient-reported outcomes (PROs), such as health status, anxiety, and depression.⁵ This is unfortunate because PROs can be used to assess the effectiveness of treatment, to enhance the quality of care and management of patients, and to help allocate resources to patients who need them the most.^{6,7} In addition, poor health status has predicted mortality and rehospitalization in patients with coronary artery disease and heart failure, independent of traditional biomedical risk factors.⁹ This information cannot be extrapolated from information standardly available in patients' medical records or from a proxy.⁷

In addition to health status, LVADs may also have an effect on psychological morbidity and feelings of worry and stress.¹⁰⁻¹⁴ Device type and settings might influence the level of psychological morbidity because patients receiving pulsa-

Received March 30, 2011; accepted August 22, 2011.

From the Department of Medical Psychology and Neuropsychology (C.B., J.D., S.S.P.), CoRPS (Center of Research on Psychology in Somatic diseases), Tilburg University, Tilburg, The Netherlands; Division Heart and Lung (N.d.J.), University Medical Center Utrecht, Utrecht, The Netherlands; Thoraxcenter, Erasmus Medical Center (K.C., S.S.P.), Rotterdam, The Netherlands; Heart Center (J.K.), St Paul's Hospital, Vancouver, British Columbia, Canada.

Correspondence to Susanne S. Pedersen, PhD, Department of Medical Psychology, CoRPS, Room P506, Tilburg University, Warandelaan 2, PO Box 90153, 5000LE Tilburg, The Netherlands. E-mail s.s.pedersen@uvt.nl

© 2011 American Heart Association, Inc.

Circ Heart Fail is available at <http://circheartfailure.ahajournals.org>

DOI: 10.1161/CIRCHEARTFAILURE.111.962472

tile LVAD therapy have a higher rate of complications and are bothered by the clicking noise from the device.¹⁵ In other heart failure populations, psychological morbidity has been associated with poor treatment adherence, poor self-efficacy, and an unhealthy lifestyle.^{15,16} Yet, it is not known whether patients receiving LVAD therapy who have psychological problems are identified and, hence, treated.

In the future, LVAD therapy is likely to be indicated as a bridge to transplantation and as destination therapy worldwide, thereby providing much optimism for the treatment of more heart failure patients in the future.¹⁷ To optimize the management of this growing group of patients, we need to know the impact of LVAD therapy on patients from a patient perspective.¹² Only with such knowledge are we able to improve care after LVAD implantation and to provide patients and families with all the necessary information that they need for effective decision making regarding whether LVAD implantation is aligned with their own preferences and goals.

Hence, the objectives of this systematic review are to provide a detailed overview of available evidence on the impact of LVAD therapy on PROs and suggest recommendations for clinical research and practice.

Methods

Literature Search

The first author (C.B.) performed a literature search on PubMed from January 1980 to May 2011 using a combination of the following search terms: *LVAD*, *left ventricular assist device*, *anxiety*, *depression*, *health status*, *quality of life*, *emotional distress*, *psychological distress*, *psychological morbidity*, and *psychosocial*. Only full-text empirical studies with a sample size ≥ 10 , examining the impact of LVAD therapy on PROs assessed by standardized clinical interviews or standardized and validated questionnaires, were eligible for inclusion. Articles found by reference searching and articles for which inclusion was questionable were checked by the last author (S.S.P.), after which a consensus was reached between both authors (C.B. and S.S.P.). Of the 250 candidate articles, 26 were identified that matched the inclusion criteria. Sixteen studies^{10–14,18–28} emanated largely from the same 4 cohorts, as reported in 1 of the other articles. From each cohort, only the most recent article was included (ie, articles with the most optimal study design and largest sample size), except for 2 extra articles that compared 2 groups of patients receiving LVAD therapy with 2 different devices.^{12,18,19,25–27} Hence, the current review is based on 16 studies (Figure).

Literature Overview

Detailed information on the 16 studies included in this review are presented in Table 1 and Table 2. The descriptive data detailed later are stratified by studies on pulsatile (Table 1) vs continuous-flow (Table 2) devices. Studies in which patients receiving therapy via both pulsatile and continuous-flow devices were included and were placed in the continuous-flow device table (Table 2).

For the pulsatile devices, the median number of patients included in the 7 studies was 30 (mean \pm SD, 36.0 \pm 27.2), with the number of patients receiving therapy via LVADs ranging from 10 to 78. The proportion of men ranged from 60% to 99%, and the mean age of study participants was 47.0 \pm 13.5 (range, 29–67) years. Three studies^{29–31} (42.9%) used a cross-sectional study design, 4 studies^{12,26,32,33} (57.1%) used a prospective (comparative) study design, of which 2 (28.6%) were a randomized controlled trial.^{26,33} In most studies, the baseline assessment was conducted before hospital discharge, which varied between 1 and 2 weeks¹² to \approx 1 month after LVAD implantation.³² The 3 cross-sectional studies used a variety of assessment times ranging from <6 weeks after implantation^{29,30} to

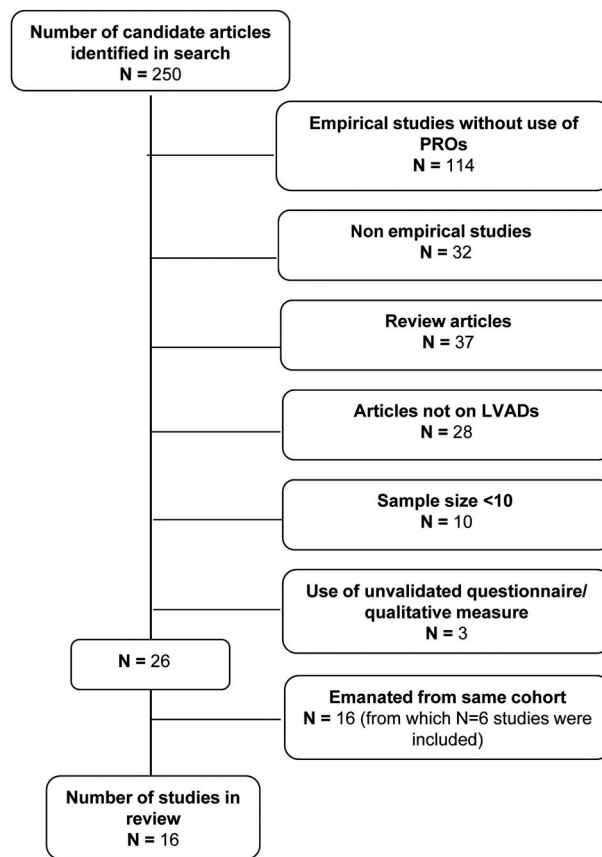


Figure. Flow chart of article selection.

up to 2 months after LVAD implantation.³¹ Two studies^{26,32} compared the PROs of LVAD patients with transplant recipients or patients receiving optimal medical treatment. Of all studies, 4 (57.1%) focused on health status,^{12,26,32,33} 2 (28.6%) on anxiety,^{30,32} and 5 (71.4%) on depression.^{26,29–32} 2 studies (28.6%) focused on both anxiety and depression.^{30,32}

For the continuous-flow devices, the median number of patients included in the 9 studies was 41 (mean \pm SD, 201 \pm 229.5), with the number of LVAD patients ranging from 17 to 655. The proportion of men ranged from 76% to 100% across studies, and the mean \pm SD age of study participants was 51.5 \pm 15.7 (range, 46–62.5) years. Two studies (22%) used a cross-sectional study design,^{19,34} 1 (11%) used a retrospective design,³⁵ and 6 (66.7%) used a prospective (comparative) study design.^{18,25,27,36–38} The baseline assessment was performed within 1 month after LVAD implantation in the prospective studies. The retrospective study³⁵ assessed PROs at 12 months after LVAD implantation, and the cross-sectional studies^{19,35} included patients ranging from 2 to 135 months after LVAD implantation. Two studies^{19,36} compared the PROs of LVAD patients with their partners or with transplant recipients. Of all studies, 8 (88.8%) focused on health status,^{18,25,27,34–38} whereas 1 study (11%) focused on depression.¹⁹

Results

PROs in Studies on Pulsatile Devices

The studies on the first generation of pulsatile LVADs (Thoratec TCI, Heartmate VE/IP [Thoratec Inc, Pleasanton, CA]; Novacor LVAS [WorldHeart Inc, Oakland, CA]; EXCOR [Berlin Heart AG, Berlin, Germany]; or Toyobo LVAD [Toyobo Ventricular Assist Systems, Toyobo, Osaka Japan]) assessed health status using a prospective design with a

Table 1. Impact of LVAD Therapy on PROs: Pulsatile Devices (7 Studies)

Study	Subtype of LVAD	No. LVAD	No. Other	Study Design*	Measure	Main Findings	% of Patients With Clinically Meaningful Change
Health status							
Dew et al (1999) ³²	Heartmate TCI/Novacor	2/8	55 OMT/97 HTx	P (2 mo)	SIP	Improvement in physical and social functioning (not all domains significant)	Not reported
Rose et al (2001) ^{24,26,28†}	Heartmate VE	68	61 OMT	P (RCT) (1 y)	SF-36, MLHFQ‡	Significant improvement in health status	Not reported
Grady et al (2004) ^{10-14,21†}	Heartmate IP/VE	78	...	P (1 y)	QLI, SIP	Total QoL (psychological/ health functioning) and functional disability better for HTx vs LVAD, psychological stressors important in LVAD patients. No significant improvement in total QoL scores over time	Not reported
Laoutaris et al (2010) ³³	EXCOR	15	...	P (RCT) (10 wk)	MLHFQ‡	Training group significantly better health status after 10 wk, no difference in control group	Not reported
Anxiety/depression							
Shapiro et al (1997) ³¹	Heartmate IP/VE	30	...	C	MMSE	Significant decrease in depression after 1 y	Not reported
Dew et al (1999) ³²	Heartmate TCI/Novacor	2/8	55 OMT/97 HTx	P (2 mo)	SLC-90	Depressive and anxiety symptoms significantly reduced over time	Not reported
Dew et al (2000) ³⁰	Heartmate VE/Novacor	19/18	...	C (1 mo)	SLC-90	Depression and anxiety significantly correlated to LVAD noise, device malfunction, infection, and driveline issues	Not reported
Rose et al (2001) ^{24,26,28†}	Heartmate VE	68	61 OMT	P (1 y)	BDI	Improved depression scores at follow-up, significantly better depression scores vs OMT	Not reported
Baba et al (2006) ²⁹	Heartmate VE/Toyobo	13/1	...	C	Diagnostic interview using DSM-IV criteria	50% of patients have ≥ 1 DSM-IV diagnosis	Not reported

DSM-IV; Diagnostic and Statistical Manual of Mental Disorders (4th Edition); HTx, transplant recipients; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MMSE, Mini-Mental State Examination; OMT, optimal medical treatment; QLI, Quality of Life Index; QoL, quality of life; SCL-90, Symptom Checklist-90; SIP, Sickness Impact Profile.

*C, cross-sectional; P, prospective; R, retrospective; RCT, randomized controlled trial.

†Multiple studies on the same study sample.

‡Disease-specific instrument.

Table 2. Impact of LVAD Therapy on PROs: Continuous-Flow Devices (9 Studies)

Study	Subtype of LVAD	No. LVAD	No. Other	Study Design*	Measure	Main Findings	% of Patients With Clinically Meaningful Change
Health status							
Siegenthaler et al (2005) ³⁷	Jarvik 2000	17	...	P (3 mo)	MLHFQ‡	Health status significantly improved	Not reported
Slaughter et al (2009) ^{27,†}	Heartmate VE/Heartmate II	66/134	...	P (2 y)	MLHFQ, ‡ KCCQ (CSS/OSS)‡	Health status improved significantly. No significant difference in health status between pulsatile and continuous devices for MLHFQ	Not reported
Allen et al (2010) ³⁵	Heartmate VE/Heartmate II	7/23	...	R	MLHFQ‡	Health status scores correlate to NYHA I-II, indicating a relatively low impact of LVAD on health status	Not reported
Rogers et al (2010) ^{18,22,23,25,27,†}	Heartmate II	655	...	P (2 y)	MLHFQ, ‡ KCCQ (CSS/OSS)‡	Health status significantly improved	79 BTT, 92 DT patients
Kugler et al (2010) ³⁶	Heartmate II	36	54 HTx	P (6 mo)	SF-36	No significant improvement in LVAD group over time, HTx group significantly better physical functioning and mental health	Not reported
Meyer et al (2010) ³⁴	Heartmate II/HVAD	17/10	...	C	SF-36	Half of health status domains significantly lower for LVAD vs general population	Not reported
Bogaev et al (2011) ^{18,22,23,25,27,†}	Heartmate II	465	...	P (6 mo)	MLHFQ, ‡ KCCQ (CSS/OSS)‡	Health status scores improved significantly. No sex difference in health status scores. Improvements in DT group higher than in BTT	Not reported
Starling et al (2011) ³⁸	Heartmate VE/Heartmate II/Thoratec pVAD	338	...	P (1 y)	EuroQoL EQ-5D	QoL significantly improved at 3–12 mo of LVAD support	Not reported
Anxiety/Depression							
Bunzel et al (2007) ^{19,20,†}	Novacor LVAS/Thoratec pVAD/DeBakey VAD/Duraheart	8/17/4/9	27 partners	C	IES-R, HADS	No significant impact	Not reported

BTT, bridge-to-transplantation therapy; CSS, Clinical Summary Score; DT, destination therapy; HADS, Hospital Anxiety and Depression Scale; HTx, transplant recipients; IES-R, Impact of Event Scale-Revised; OSS, Overall Summary Score; QoL, quality of life.

*C, cross-sectional; P, prospective; R, retrospective.

†Multiple studies on the same study sample.

‡Disease-specific instrument.

variety of instruments (Table 1). All studies found a significant improvement in the mean health status score (ie, the Minnesota Living with Heart Failure Questionnaire [MLHFQ]) or in at least 2 subdomain scores (ie, the Short-Form Health Survey 36 [SF-36], the Sickness Impact Profile, the LVAD Stressor Scale, and the Quality of Life Index [QoL Index]) at follow-up compared with baseline. The improvement in health status seemed to reach a plateau at ≈ 3 months after LVAD implantation. The results showed that, during this period, physical disability becomes less prominent and patients feel less fatigued and sleep better, thereby increasing the ability of self-care and ambulation.¹² The impact of the degree of physical disability on health status was also indicated in a recent trial that randomized LVAD patients to an exercise training program versus usual-care. The outcomes demonstrated that improvement in physical exercise capacity in patients in the treatment arm led to a better health status compared with that of the patients in the control arm.³³ Despite improvements in physical functioning, many patients may experience psychosocial problems and impaired psychological well-being, especially at ≈ 1 month after implantation.^{12,21} The psychological symptoms seem to originate from feelings of sadness, helplessness, irritability, feeling useless to others, and having a sense of loss of control over one's life^{12,21}; and seem to be associated with worrying about LVAD malfunction, complications, waiting for a donor heart, and being away from family.¹² Depression and anxiety are correlated with LVAD noise, driveline problems, and infection ($P < 0.05$ for all).³⁰ The prevalence rates of anxiety and depression varied widely across the 6 studies that included a semistructured diagnostic interview using Diagnostic and Statistical Manual of Mental Disorders (4th Edition) criteria, the Symptom Checklist-90, the Beck Depression Inventory, or the Mini-Mental State Examination (Table 2). Some studies found that only 2% of LVAD patients experienced depression and only 4% experienced anxiety,²⁰ whereas others found a considerable group of LVAD patients experiencing a depressive or adjustment disorder (21% and 37%–50%, respectively).^{29,31} In trials (ie, the Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure trial) comparing LVAD patients using pulsatile devices with patients using optimal medical treatment and transplant recipients, LVAD support was associated with a significant improvement in health status and depressive symptoms in contrast to medication alone ($P < 0.05$ for both).^{26,30,32} However, LVAD patients do not seem to attain the same level of health status compared with transplant recipients, with transplant recipients experiencing more improvements in mobility, self-care ability, physical ability, and social functioning than LVAD patients.^{13,32} Health status instruments did not show a statistically significant difference between patient groups, and all health status domains were not significantly better or worse when a difference existed between groups.

PROs in Studies on Continuous-Flow Devices

The most intensively studied continuous-flow device used in the studies included for the review was the HeartMate II (Thoratec Inc). Other devices included the Micromed DeBakey

(Micromed Cardiovascular Inc, Houston, TX), INCORE (Berlin Heart AG), Jarvik 2000 (Jarvik Heart, Inc, New York, NY), or HVAD device (HeartWare Inc, Framingham, MA) (Table 2). Almost all studies on patients with a continuous-flow LVAD show significant improvements in mean health status scores, using the MLHFQ, Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-36, and EuroQol EQ-5D (EQ-5D), from baseline up to the 3-, 6-, and 12-month follow-up ($P < 0.05$ for all).^{18,25,27,34,35,37,38} Only the study by Kugler et al³⁶ found no significant improvement in health status using the SF-36 at the 6-month follow-up. Whether this was due to psychosocial problems or a lower physical exercise tolerance is not clear, because both may ultimately restrict patients' opportunities to re-engage in professional and recreational activities, which are known predictors for long-term health status.³⁶

In recent years, several articles have been published on comparative studies between LVAD patients with different devices and in different clinical settings^{25,27,34,38} or between LVAD patients and transplant recipients and healthy controls.^{34,36} The HeartMate II trial had 2 arms that enabled the investigators to analyze the health status within and between patient groups supported by the HeartMate XVE or the HeartMate II. At the 12-month follow-up, the health status of patients receiving therapy via continuous-flow LVADs was better compared with those receiving therapy via pulsatile devices (MLHFQ, $P = 0.03$; KCCC-OSS [Overall Summary Score], $P = 0.06$; KCCQ-CSS [Clinical Summary Score], $P = 0.12$), likely caused by the improved durability, decrease in complications, smaller size, and silent operation of the continuous-flow device.²⁷ Recently, the HeartMate II was also compared with the HeartMate XVE and the Thoratec pVAD in a commercial setting to investigate the relative efficacy and risk profile, in patients enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support. Health status appeared to improve equally for the 2 groups of devices ($P < 0.001$) after 3 months to 1 year.³⁸ Patients receiving therapy via pulsatile and continuous-flow devices were not significantly different on symptoms of anxiety, depression, and posttraumatic stress disorder.¹⁹ The cross-sectional study of Meyer et al³⁴ found no significant differences in domain scores between 2 continuous-flow systems: the centrifugal-flow pump Heartmate II and the axial-flow pump HVAD.

From both arms of the HeartMate II trial, patients were also selected based on their device indication (ie, bridge-to-transplant or destination therapy) and compared on paired health status scores. The group of LVAD patients indicated for destination therapy had a higher improvement in median health status scores between baseline and 6 months than the group of LVAD patients indicated for bridge-to-transplant therapy (MLHFQ, -40 vs -29 points; KCCC-OSS, 39 vs 28 points; KCCQ-CSS, 36 vs 24 points, respectively).²⁵ In this study, 79% of the bridge-to-transplant patients and 92% of the destination therapy patients with paired data had achieved a clinically meaningful improvement of > 5 points in their KCCC-OSS and KCCQ-CSS scores compared with baseline.²⁵

Compared with transplant recipients and healthy controls, LVAD patients reported considerably poorer health status at

baseline ($P=0.0032$) and at the 6-month follow-up ($P=0.016$), especially with respect to mental health and physical functioning^{34,36} and with respect to the social functioning, role physical functioning, and role emotional functioning domains of the SF-36.³⁴

Overall, evidence on the impact of the duration of living with an LVAD, the initial diagnosis, and sex and age disparities in health status is scarce among LVAD patients. Women tend to have been underrepresented in LVAD studies, with one study finding no significant sex differences among LVAD patients (MLHFQ, $P=0.661$; KCCQ-OSS, $P=0.706$; KCCQ-CSS, $P=0.371$).¹⁸

Discussion

Summary of the Findings

This review indicates that LVAD patients experience an improvement in health status, particularly in the first 3 months after LVAD implantation and discharge. This trend was visible irrespective of the type of device (pulsatile vs continuous-flow devices) and clinical setting (destination and bridge-to-transplant therapy). Results also indicated that LVAD patients supported by continuous-flow devices and destination therapy show the greatest improvements in health status after implantation.

Few studies have examined the prevalence of anxiety and depression in LVAD patients, in particular in patients receiving therapy via continuous-flow LVADs. Patients supported by pulsatile devices showed relatively high mean depression scores just after LVAD implantation.^{26,29,31} The retrospective study¹⁹ of Bunzel et al²⁰ found no significant difference in depression scores between patients receiving therapy via pulsatile vs continuous-flow devices; these patients might be more vulnerable to psychological distress, based on the higher rate of complications and the characteristics of the device (eg, short durability, large size, noise, and large batteries). Hence, these differences in findings could well be explained by sample size limitations, differences in subtype of devices, and the time of collecting data.

The LVAD patients report better health status and fewer symptoms of anxiety and depression when compared with their partners and with patients receiving optimal medical treatment, but not when compared with transplant recipients. In contrast to transplant recipients, LVAD patients are recurrently reminded of their device because of the need to clean the driveline insertion site and change batteries frequently.¹⁵ Furthermore, organ recipients appear to redefine “normal” life and what it entails after transplantation.³²

Overall, there was a substantial difference between the studies in the handling and reporting of PROs, depending on whether PROs were assessed as primary or secondary outcomes. In Table 3, the details on the number of patients alive from baseline to end of follow-up, the estimated percentage of those patients having PRO data, and the cause of missing data were outlined for all prospective studies assessing health status in LVAD patients. Except for the Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure trial,²⁶ all studies on pulsatile devices assessed health status as a primary outcome, whereas this

only holds true for 1 continuous-flow study.³⁶ The percentage of PRO data obtained from the patients alive over time was 92% to 100% in the pulsatile device studies and 46% to 91% in the continuous-flow device studies. At the end of the full study, this percentage was unchanged for the pulsatile device studies and was 49% to 89% for the continuous-flow device studies. In 2 continuous-flow device studies, the follow-up period for the PROs was shorter than the follow-up period for the full study, causing an absence of PRO data at the final time points.^{18,25} For those studies, the percentage of PRO data obtained was calculated based on the number of patients alive at the end of the PRO follow-up period rather than at the end of the full study. Most studies indicated similar reasons for the missing data (eg, patient exclusion, deceased, too ill, heart transplantation, or dropout). None of the studies reported cognitive limitations or psychological distress as a reason for missing data.

Limitations of the Review

Because of the different time era of the studies included in this review and the heterogeneity of the studies (differences in follow-up assessments, sample sizes, and PRO assessment), it was not possible to perform a formal meta-analysis. Although increasing the statistical power of the findings by excluding studies with a small sample size ($N<10$), this resulted in fewer articles eligible for inclusion. In turn, this could have potentially created a bias toward results found in larger studies. The proportion of female patients across studies was relatively low; hence, it is not feasible to generalize the findings to women with an LVAD. There was a considerable difference in the percentage of missing PRO data between the pulsatile and continuous-flow device studies. This is most probably caused by the fact that most of the pulsatile device studies assessed PROs as primary outcomes but was also because of shorter follow-up times, thereby decreasing the chance of death, heart transplantation, and drop out. Only 3 studies^{18,36,37} reported how they dealt with loss of data, which included comparing the baseline characteristics of patients for whom data were and were not available or substituting the missing scores by the maximum negative score of the used instrument. Correcting for missing data did not affect the outcomes in these studies. Other studies calculated the percentage and significance of improvement by simply comparing the group total scores of patients with paired data between baseline and follow-up. However, the number of patients with paired data decreases significantly over time, which may increase the probability of finding a significant improvement because the sicker patients are usually lost to follow-up. More information is needed on intraindividual changes and the proportion of patients who experience a clinically relevant change.

Moreover, the instruments chosen for the study might not have been sufficiently sensitive to tap LVAD-related changes in health status, if present.³⁶ Some instruments, such as the KCCQ, have also not been used optimally, because authors did not report subdomain scores. Finally, studies failed to examine key predictors of intraindividual changes in PROs over time or associations between PROs and other outcomes, such as mortality and number of hospitalizations.

Table 3. Overview of Sample Size, Follow-Up, and Missing Data of LVAD Studies With Health Status Assessments

Study	No. Other	Maximum PRO Follow-Up Reported*	Baseline	No. of LVAD Study Patients Alive Over Time						Mean % of Living Patients With PRO Data Overall	% of Living Patients With PRO Data at the End of Follow-Up	Reason for Missing Data at Inclusion and Follow-Up	Information on Handling of Missing Data
				2 mo	3 mo	6 mo	1 y	2 y					
Pulsatile devices													
Dew et al (1999) ³²	55 OMT/97 HTx	P (2 mo)	10	10	All patients	All patients	HTx, too ill, refused, or language issue	No
Rose et al (2001) ^{24,26,28†}	61 OMT	P (RCT) (1 y)	68	...	38	24	5	5	92.0	92.0	92.0	Deceased, too ill, or no transportation	No
Grady et al (2004) ^{10-14,21†}	...	P (1 y)	78	...	43	9	All patients	All patients	HTx, too ill, refused, or deceased	No
Laoutaris et al (2010) ²⁵	...	P (RCT) (10 wk)	15	All patients	All patients	...	No
Continuous-flow devices													
Siegenthaler et al (2005) ³⁷	...	P (3 mo)	17	...	11	7	4	4	61.3	75.0	75.0	Deceased	Yes
Slaughter et al (2009) ^{18,22,23,25,27†}	...	P (2 y)	200	...	127	101	64	64	77.6	60.5	60.5	Deceased, HTx	No
Rogers et al (2010) ^{18,22,23,25,27†}	...	P (2 y)	655	...	460	213 (only DT)	101 (only DT)	101 (only DT)	82.5 BTT, 90.7 DT	82.8 BTT, 88.5 DT	82.8 BTT, 88.5 DT	Deceased, HTx, staff availability, scheduling	No
Kugler et al (2010) ³⁶	54 HTx	P (6 mo)	36	...	34	75.0	64.3	64.3	Deceased, refused, or dropped out	Yes
Bogaev et al (2011) ^{18,22,23,25,27†}	...	P (6 mo)	465	...	251	150	121 (18 mo)	121 (18 mo)	79.5	85.1	85.1	Deceased, HTx, staff availability	Yes
Starling et al (2011) ³⁸	...	P (1 y)	338	...	306	196	128	...	46.1	48.4	48.4	Not reported	No

BTT, bridge-to-transplantation therapy; DT, destination therapy; HTx, heart transplantation; OMT, optimal medical treatment.

*C, cross-sectional; P, prospective; R, retrospective; RCT, randomized controlled trial.

†Multiple studies on the same study sample.

Table 4. Recommendations for the Incorporation of PRO Assessments in Clinical Practice and Future Research

Variable	Clinical Practice	Future Research
Purpose of incorporating PROs in clinical practice and research	PROs have unique prognostic value beyond physician-rated measures and information derived from patients' medical status	Evaluate the impact of treatment, devices, and device settings on PROs using both health status and anxiety/depression measures
	Inclusion of the patient perspective; no proxy measure available from measures assessed in a standard clinical setting	Comparison of PROs between LVAD patients and other groups (eg, patients receiving optimal medical treatment, HTx) is necessary for informed political and clinical decision making
	PROs may facilitate communication between patients and physicians	Compare the sensitivity of disease-specific and generic PRO measures to detect changes over time; if necessary, develop new disease-specific measures (eg, to assess anxiety and depression)
	PROs may enhance identification of high-risk patients whose medical treatment needs to be optimized	
	PROs can be used as performance measures to evaluate the quality of care	
Recommendations for PROs as primary outcomes in LVAD research and therapy	Enables more accurate tracking of changes in patient's physical and psychological functioning over time and better coordination of care (eg, individually tailored rehabilitation programs)	Examine the correlation between clinical variables and PROs and determine their relative importance for LVAD patient prognosis
	A no-risk, low-cost, and low-burden addition to clinical care	Use both an interindividual and intraindividual approach in data analyses
		Adhere to CONSORT and STROBE statement guidelines for reporting critical PRO data elements (eg, missing data and clinically meaningful improvement)
		Use of disease-specific questionnaires (eg, MLHFQ, KCCQ) in studies with LVAD cohorts only
	Incorporate PRO instruments for anxiety and depression in studies on continuous-flow devices	
		Use prospective studies with large sample sizes

CONSORT, Consolidated Standards of Reporting Trials; MLHFQ, Minnesota Living with Heart Failure Questionnaire; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Need for Assessing PROs in LVAD Patients

The importance of studying PROs, such as health status, is gaining increased recognition because of the belief that an illness, its treatment, and complications affect all domains of a patient's life and that the patient perspective is as valid as that of the clinician when evaluating outcomes.³⁹ In addition, information on PROs is important for future patients and families who have to make an informed decision regarding the option for LVAD therapy. Information on PROs cannot be extracted from patients' medical records or a proxy and, therefore, PROs need to be assessed in their own right. Thus, PROs may provide important additional information to health care providers and serve as targets for intervention in individual patients.⁸

Despite their importance, there is often a minor emphasis placed on PROs, and they are rarely included as primary outcomes in clinical LVAD trials.⁶ In particular, studies on continuous-flow LVADs show a tendency to neglect anxiety and depression. This is surprising given that 15% to 36% of patients with heart failure experience depression,^{40,41} 40% experience anxiety,¹⁶ and 10% to 17% experience posttraumatic stress disorder.^{42,43} Symptoms of depression and anxiety can be disabling¹⁵ and are associated with an increased risk of declines in physical health,¹⁶ mortality, higher medication costs,¹⁵ noncompliance with treatment, malignancies,^{44,45} and hospital readmissions.⁸ The limited available

evidence suggests that there may be a link between LVAD technology and the patient's psychological adjustment.⁵

Recommendations for Future Research and Care of LVAD Patients

Because it has been widely established that LVAD therapy is capable of enhancing the survival of patients with end-stage heart failure, measuring PROs (eg, functional status, quality of life, and psychological distress) in these patients deserves a priority similar to survival in future LVAD studies. This review indicates that PROs improve over time, yet it also uncovers major shortcomings in their assessment, reflecting a considerable knowledge gap in the optimal care for these patients. More specific recommendations for future research and clinical practice in LVAD therapy are given in Table 4.

In addition to the current interindividual approach (comparing changes in mean group scores over time), PROs should also be analyzed using an intraindividual approach focusing on the proportion of patients who experience a clinical improvement or deterioration over time. Eventually, this will create the possibility of risk stratifying patients and enhancing optimal clinical practice.

Appropriate care should also be given when selecting PRO measures, with a distinct preference for disease-specific measures, such as the KCCQ or MLHFQ. Patients are more likely to

identify themselves in these instruments, thereby increasing the response rate. In studies on continuous-flow devices, health status was predominantly measured with the KCCQ or the MLHFQ, with both measures showing similar results in various large-scale LVAD studies.^{18,22,23,25,27} This suggests that these measures are sensitive for detecting LVAD-related changes in health status over time, if present. To capture psychological morbidity in LVAD patients, the Heart Failure Symptom Checklist or LVAD Stressor Scale could be used in addition to specific anxiety/depression measures. Given the paucity of studies on psychological functioning in LVAD patients, it is difficult to recommend a specific instrument to use. The Patient Health Questionnaire [PHQ-9] and the Generalized Anxiety Disorder [GAD-7] Scale might be a way to start, because both instruments have excellent psychometric properties. In addition, these measures are exempt from copyright and can be used free of charge.

It is paramount that future studies comply with the Consolidated Standards of Reporting Trials [CONSORT] and the Strengthening the Reporting of Observational studies in Epidemiology [STROBE] statements for reporting results of randomized trials and observational studies.^{46,47} These guidelines also stipulate reporting of missing data and clinical relevance, as has also been advocated by others.^{48,49} This is needed because, for sufficiently large trials, it is possible to have a statistically significant difference that may not be clinically meaningful.⁴⁹ In clinical practice, there needs to be a shift in LVAD rehabilitation programs from survival to also focus on coping abilities and health status of LVAD patients. These programs need to be tailored to the individual patient and should also account for the patient's level of emotional functioning.

Conclusion

There is a paucity of studies on the patient perspective of LVAD therapy. Initial evidence suggests an improvement in health status, anxiety, and depression in the first months after LVAD implantation. However, PRO scores of LVAD patients are still lower for physical, social, and emotional functioning compared with transplant recipients. To advance the field of LVAD research and to optimize the management of an increasingly growing population of LVAD patients, more well-designed large-scale studies on PROs are needed. By these studies, we will be able to further elucidate the psychological and social impact of LVAD therapy, thereby creating the opportunity to improve the care for patients after LVAD implantation and to provide important information that is needed by patients and families for effective decision making regarding whether LVAD implantation is aligned with their own preferences and goals.

Sources of Funding

This research was in part supported with a VIDI grant (91710393) from the Netherlands Organization for Health Research and Development, The Hague, The Netherlands (Dr Pedersen).

Disclosures

None.

References

- Douglas P, Morgan C, Lee H, Foster FR. LVAD as destination therapy: the economic dilemma. *IEEE Technol Soc Magazine*. 2004;23:23–27.
- Christiansen S, Klocke A, Autschbach R. Past, present, and future of long-term mechanical cardiac support in adults. *J Card Surg*. 2008;23:664–676.
- Leff JD, Shore-Lesserson L. Left ventricular assist devices: an evolving state of the art. *Semin Cardiothorac Vasc Anesth*. 2010;14:21–23.
- Krishnamani R, DeNofrio D, Konstam MA. Emerging ventricular assist devices for long-term cardiac support. *Nat Rev Cardiol*. 2010;7:71–76.
- Samuels LE, Holmes EC, Petrucci R. Psychosocial and sexual concerns of patients with implantable left ventricular assist devices: a pilot study. *J Thorac Cardiovasc Surg*. 2004;127:1432–1435.
- Spertus JA. Evolving applications for patient-centered health status measures. *Circulation*. 2008;118:2103–2110.
- Krumholz HM, Peterson ED, Ayanian JZ, Chin MH, DeBusk RF, Goldman L, Kiefe CI, Powe NR, Rumsfeld JS, Spertus JA, Weintraub WS. Report of the National Heart, Lung, and Blood Institute working group on outcomes research in cardiovascular disease. *Circulation*. 2005;111:3158–3166.
- Mommersteeg PM, Denollet J, Spertus JA, Pedersen SS. Health status as a risk factor in cardiovascular disease: a systematic review of current evidence. *Am Heart J*. 2009;157:208–218.
- Weintraub WS, Spertus JA, Kolm P, Maron DJ, Jurkovic Z, Zhang Z, Hartigan PM, Lewis C, Veledar E, Bowen J, Dunbar SB, Deaton C, Kaufman S, O'Rourke RA, Goeree R, Barnett PG, Teo KK, Boden WE, Mancini GB. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med*. 2008;359:677–687.
- Grady KL, Meyer P, Mattea A, Dressler D, Ormaza S, White-Williams C, Chillcott S, Kaan A, Loo A, Todd B, Klemme A, Piccione W, Costanzo M. Change in physical and psychosocial domains of quality of life from before to after discharge post left ventricular assist device implantation. *J Heart Lung Transplant*. 2001;20:203.
- Grady KL, Meyer P, Mattea A, White-Williams C, Ormaza S, Kaan A, Todd B, Chillcott S, Dressler D, Fu A, Piccione W Jr, Costanzo MR. Improvement in quality of life outcomes 2 weeks after left ventricular assist device implantation. *J Heart Lung Transplant*. 2001;20:657–669.
- Grady KL, Meyer PM, Dressler D, Mattea A, Chillcott S, Loo A, White-Williams C, Todd B, Ormaza S, Kaan A, Costanzo MR, Piccione W. Longitudinal change in quality of life and impact on survival after left ventricular assist device implantation. *Ann Thorac Surg*. 2004;77:1321–1327.
- Grady KL, Meyer PM, Dressler D, White-Williams C, Kaan A, Mattea A, Ormaza S, Chillcott S, Loo A, Todd B, Costanzo MR, Piccione W. Change in quality of life from after left ventricular assist device implantation to after heart transplantation. *J Heart Lung Transplant*. 2003;22:1254–1267.
- Grady KL, Meyer PM, Mattea A, Dressler D, Ormaza S, White-Williams C, Chillcott S, Kaan A, Loo A, Todd B, Klemme A, Piccione W, Costanzo MR. Change in quality of life from before to after discharge following left ventricular assist device implantation. *J Heart Lung Transplant*. 2003;22:322–333.
- Eshelman AK, Mason S, Neme H, Williams C. LVAD destination therapy: applying what we know about psychiatric evaluation and management from cardiac failure and transplant. *Heart Fail Rev*. 2009;14:21–28.
- Konstam V, Moser DK, De Jong MJ. Depression and anxiety in heart failure. *J Card Fail*. 2005;11:455–463.
- Slaughter MS, Meyer AL, Birks EJ. Destination therapy with left ventricular assist devices: patient selection and outcomes. *Curr Opin Cardiol*. 2011;26:232–236.
- Bogaev RC, Pamboukian SV, Moore SA, Chen L, John R, Boyle AJ, Sundareswaran KS, Farrar DJ, Frazier OH. Comparison of outcomes in women versus men using a continuous-flow left ventricular assist device as a bridge to transplantation. *J Heart Lung Transplant*. 2011;30:515–522.
- Bunzel B, Laederach-Hofmann K, Wieselthaler G, Roethy W, Wolner E. Mechanical circulatory support as a bridge to heart transplantation: what remains? Long-term emotional sequelae in patients and spouses. *J Heart Lung Transplant*. 2007;26:384–389.
- Bunzel B, Laederach-Hofmann K, Wieselthaler GM, Roethy W, Drees G. Posttraumatic stress disorder after implantation of a mechanical assist device followed by heart transplantation: evaluation of patients and partners. *Transplant Proc*. 2005;37:1365–1368.
- Grady KL, Meyer P, Mattea A, Dressler D, Ormaza S, White-Williams C, Chillcott S, Kaan A, Todd B, Loo A, Klemme AL, Piccione W, Costanzo MR. Predictors of quality of life at 1 month after implantation of a left ventricular assist device. *Am J Crit Care*. 2002;11:345–352.

22. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, Conte JV, Naka Y, Mancini D, Delgado RM, MacGillivray TE, Farrar DJ, Frazier OH. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med*. 2007;357:885–896.
23. Pagani FD, Miller LW, Russell SD, Aaronson KD, John R, Boyle AJ, Conte JV, Bogaev RC, MacGillivray TE, Naka Y, Mancini D, Massey HT, Chen L, Klodell CT, Aranda JM, Moazami N, Ewald GA, Farrar DJ, Frazier OH. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol*. 2009;54:312–321.
24. Park SJ, Tector A, Piccioni W, Raines E, Gelijns A, Moskowitz A, Rose E, Holman W, Furukawa S, Frazier OH, Dembitsky W. Left ventricular assist devices as destination therapy: a new look at survival. *J Thorac Cardiovasc Surg*. 2005;129:9–17.
25. Rogers JG, Aaronson KD, Boyle AJ, Russell SD, Milano CA, Pagani FD, Edwards BS, Park S, John R, Conte JV, Farrar DJ, Slaughter MS. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. *J Am Coll Cardiol*. 2010;55:1826–1834.
26. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345:1435–1443.
27. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatoes AJ, Delgado RM III, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009;361:2241–2251.
28. Stevenson LW, Miller LW, Desvigne-Nickens P, Ascheim DD, Parides MK, Renlund DG, Oren RM, Krueger SK, Costanzo MR, Wann LS, Levitan RG, Mancini D. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). *Circulation*. 2004;110:975–981.
29. Baba A, Hirata G, Yokoyama F, Kenmoku K, Tsuchiya M, Kyo S, Toyoshima R. Psychiatric problems of heart transplant candidates with left ventricular assist devices. *J Artif Organs*. 2006;9:203–208.
30. Dew MA, Kormos RL, Winowich S, Stanford EA, Carozza L, Borovetz HS, Griffith BP. Human factors issues in ventricular assist device recipients and their family caregivers. *ASAIO J*. 2000;46:367–373.
31. Shapiro PA, Levin HR, Oz MC. Left ventricular assist devices: psychosocial burden and implications for heart transplant programs. *Gen Hosp Psychiatry*. 1996;18:305–355.
32. Dew MA, Kormos RL, Winowich S, Nastala CJ, Borovetz HS, Roth LH, Sanchez J, Griffith BP. Quality of life outcomes in left ventricular assist system inpatients and outpatients. *ASAIO J*. 1999;45:218–225.
33. Laoutaris ID, Dritsas A, Adamopoulos S, Manginas A, Gouziouta A, Kallistratos MS, Kouloupoulou M, Voudris V, Cokkinos DV, Sfrakias P. Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. *Eur J Cardiovasc Prev Rehabil*. 2011;18:33–40.
34. Meyer AL, Kugler C, Malehsa D, Haverich A, Strueber M. Patient satisfaction with the external equipment of implantable left ventricular assist devices. *Artif Organs*. 2010;34:721–725.
35. Allen JG, Weiss ES, Schaffer JM, Patel ND, Ullrich SL, Russell SD, Shah AS, Conte JV. Quality of life and functional status in patients surviving 12 months after left ventricular assist device implantation. *J Heart Lung Transplant*. 2010;29:278–285.
36. Kugler C, Malehsa D, Tegtbur U, Guetzlaff E, Meyer AL, Bara C, Haverich A, Strueber M. Health-related quality of life and exercise tolerance in recipients of heart transplants and left ventricular assist devices: a prospective, comparative study. *J Heart Lung Transplant*. 2010;30:204–210.
37. Siegenthaler MP, Westaby S, Frazier OH, Martin J, Banning A, Robson D, Pepper J, Poole-Wilson P, Beyersdorf F. Advanced heart failure: feasibility study of long-term continuous axial flow pump support. *Eur Heart J*. 2005;26:1031–1038.
38. Starling RC, Naka Y, Boyle AJ, Gonzalez-Stawinski G, John R, Jorde U, Russell SD, Conte JV, Aaronson KD, McGee EC Jr, Cotts WG, Denofrio D, Pham DT, Farrar DJ, Pagani FD. Results of the post-US Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol*. 2011;57:1890–1898.
39. Leplege A, Hunt S. The problem of quality of life in medicine. *JAMA*. 1997;278:47–50.
40. Kop WJ, Synowski SJ, Gottlieb SS. Depression in heart failure: biobehavioral mechanisms. *Heart Fail Clin*. 2011;7:23–38.
41. Pasic J, Levy WC, Sullivan MD. Cytokines in depression and heart failure. *Psychosom Med*. 2003;65:181–193.
42. Ladwig KH, Baumert J, Marten-Mittag B, Kolb C, Zrenner B, Schmitt C. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: results from the prospective living with an implanted cardioverter-defibrillator study. *Arch Gen Psychiatry*. 2008;65:1324–1330.
43. Von Kanel R, Kraemer B, Saner H, Schmid JP, Abbas CC, Begre S. Posttraumatic stress disorder and dyslipidemia: previous research and novel findings from patients with PTSD caused by myocardial infarction. *World J Biol Psychiatry*. 2010;11:141–147.
44. Favaro A, Gerosa G, Caforio ALP, Volpe B, Rupolo G, Zarneri D, Boscolo S, Pavan C, Tenconi E, Agostino C, Moz M, Torregrossa G, Feltrin G, Gambino A, Santonastaso P. Posttraumatic stress disorder and depression in heart transplantation recipients: the relationship with outcome and adherence to medical treatment. *Gen Hosp Psychiatry*. 2011;33:1–7.
45. Dew MA, Kormos RL, Roth LH, Murali S, DiMartini A, Griffith BP. Early post-transplant medical compliance and mental health predict physical morbidity and mortality one to three years after heart transplantation. *J Heart Lung Transplant*. 1999;18:549–562.
46. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *J Pharmacol Pharmacother*. 2010;1:100–107.
47. von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344–349.
48. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol*. 1993;71:1106–1107.
49. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Pina I, Tooley J, Weintraub WS, Rumsfeld JS. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J*. 2005;150:707–715.

CLINICAL PERSPECTIVE

Evidence suggests that patients receiving left ventricular assist device (LVAD) therapy experience an improvement in health status over time, independent of device type and setting. However, although their physical disability becomes less prominent after implantation, many patients experience difficulties with psychological adjustment, especially early after implantation, which is associated with worrying about LVAD malfunction, complications, waiting for a donor heart, and being away from family. Furthermore, overall functioning of LVAD patients is still more impaired compared with transplant recipients on physical, social, and emotional functioning. Extensive information on patient-reported outcomes in LVAD patients is limited, with many of the existing studies having methodological shortcomings. To advance the field of LVAD research and to optimize the care of an increasingly growing population of LVAD patients, more well-designed large-scale studies are needed to further elucidate the impact of LVAD therapy on patient-reported outcomes.

Patient-Reported Outcomes in Left Ventricular Assist Device Therapy: A Systematic Review and Recommendations for Clinical Research and Practice

Corline Brouwers, Johan Denollet, Nicolaas de Jonge, Kadir Caliskan, Jennifer Kealy and
Susanne S. Pedersen

Circ Heart Fail. 2011;4:714-723; originally published online September 9, 2011;
doi: 10.1161/CIRCHEARTFAILURE.111.962472

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX
75231

Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://circheartfailure.ahajournals.org/content/4/6/714>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Heart Failure* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation: Heart Failure* is online at:
<http://circheartfailure.ahajournals.org/subscriptions/>